Lee, Y.S., Challis, B.G., Thompson, D.A., Yeo, G.S.H., Keogh, J.M., Madonna, M.E., Wraight, V., Sims, M., Vatin, V., Meyre, D., et al. (2006). Cell Metab. *3*, this issue, 135–140.

Maes, H.H., Neale, M.C., and Eaves, L.J. (1997). Behav. Genet. *27*, 325–351.

Seidah, N.G., and Chretien, M. (1994). Methods Enzymol. *244*, 175–188.

Ste Marie, L., Miura, G.I., Marsh, D.J., Yagaloff, K., and Palmiter, R.D. (2000). Proc. Natl. Acad. Sci. USA *97*, 12339–12344.

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# Unlikely partners in weight loss?

**The classic role of bile acids is as a key component of cholesterol homeostasis. New evidence recently published in *Nature* (Watanabe et al., 2006), however, describes a bile acid signaling pathway that controls energy expenditure through induction of thyroid hormone signaling pathways. This work may point to new approaches to tissue-specific metabolic regulation.**

Maintenance of normal serum cholesterol levels is essential for life. Excess cholesterol is eliminated by hepatic conversion to soluble bile acids (BAs), which are excreted into the small intestine. Most of the BA pool, however, is subsequently reabsorbed and recycled through the enterohepatic circulation. The production of BAs from cholesterol is regulated by the farnesoid X receptor (FXR), which when bound by BAs ultimately reduces expression of cholesterol 7 $\alpha$-hydroxylase, the rate-limiting enzyme in BA synthesis (for review, see Kalaany and Mangelsdorf [2005]).

In addition to acting through this classic nuclear hormone signaling pathway, BAs have also been shown to signal in an FXR-independent manner by binding to a novel G protein-coupled cell-surface receptor, termed TGR5 (Maruyama et al., 2002). Activation of TGR5 leads to increased intracellular cAMP production, which modifies macrophage function (Kawamata et al., 2003). Now a landmark paper recently published in *Nature* by Watanabe et al. (2006) describes an FXR-independent role for BAs in controlling energy expenditure (EE). The authors demonstrate that BAs increase EE in brown adipose tissue of mice, resulting in prevention of diet-induced obesity and insulin resistance. Based on in vitro studies in human skeletal myocytes, they postulate that bile acids would also increase EE in man.

The novel role for BAs in regulating cellular metabolism as described by Watanabe et al. (2006) is illustrated in Figure 1. BAs bind to the TGR5 receptor (coupled to $G_s$), which leads to increased intracellular cAMP production and induction of the *Dio2* gene whose gene product is type 2 iodothyronine deiodinase or D2. Several major BAs such as cholic acid, deoxycholic acid, and chenodeoxycholic acid activate this pathway, but a synthetic FXR agonist, GW4064, has no effect. BAs induce D2 expression in thermogenically important tissues such as murine brown fat and human skeletal myocytes, because only these tissues express both TGR5 and D2. D2 then converts locally available $T_4$ to $T_3$, without leading to an increase in circulating thyroid hormone levels, resulting in an increase in oxygen consumption and EE. In addition to D2, several genes involved in EE were increased in brown adipose tissue after BA treatment: peroxisome proliferator-activated receptor $\gamma$ coactivator-1$\alpha$ and -1$\beta$, uncoupling protein (UCP) 1 and 3, straight chain acyl-CoA oxidase 1, and muscle carnitine palmitoyltransferase. The increase in D2 expression, however, is essential for the increase in EE by BAs, since diet-induced obesity is prevented in wild-type but not D2 knockout mice after BA treatment.

A high-fat diet also increases D2 expression in brown adipose tissue, but this effect appears to be downstream from TGR5 (see Figure 1), since cAMP levels are not increased to the same extent as D2 levels by this diet. BAs increase cAMP and D2 levels in brown adipose tissue, but these effects are much more pronounced in tissue obtained from mice fed a high-fat diet rather than fed a regular diet. The authors point out that this might explain why BAs prevent diet-induced obesity but do not affect the bodyweight of animals fed a regular diet. Thus, the BA effect is specific to thermogenic tissues and is observed only when mice are fed a high-fat diet.

Exactly how $T_3$, produced locally by D2, mediates an increase in oxygen consumption and EE in murine brown adipose tissue or human skeletal muscle remains to be clarified. One potential mechanism is $T_3$-mediated induction of UCP expression. UCPs dissipate the proton gradient generated by the electron transport chain as heat resulting in a reduction in ATP synthesis. Since both $T_3$ and cAMP are known to increase expression of UCP1 in brown adipose tissue (Ribeiro et al., 2001), this could potentially explain the increase in EE observed in mice treated with BAs. In contrast, fat-free body mass, which is predominantly skeletal muscle, is the major determinant of basal metabolism in humans, which lack significant amounts of brown adipose tissue (except in the neonatal period; Ravussin et al., 1986). Importantly, skeletal muscle UCP3 expression is positively correlated with EE in the Pima Indians, increased by $T_3$, and decreased in type 2 diabetics (for review, see Hesselink and Schrauwen [2005]). Thus like UCP1, UCP3 induction in skeletal muscle might mediate an increase in EE in humans after BA treatment promoting weight loss and insulin sensitivity.

The mechanism(s) by which BAs increase EE, however, is likely to be more complex than noted above. For example, in the 1930s, patients given the artificial uncoupler of oxidative phosphorylation, 2,4 dinitrophenol (DNP), at low to moderate doses demonstrated significant weight loss without associated increases in urinary nitrogen excretion or heart rate (for review, see Harper et al. [2001]). Higher doses of DNP, in contrast, were associated with cataract formation and

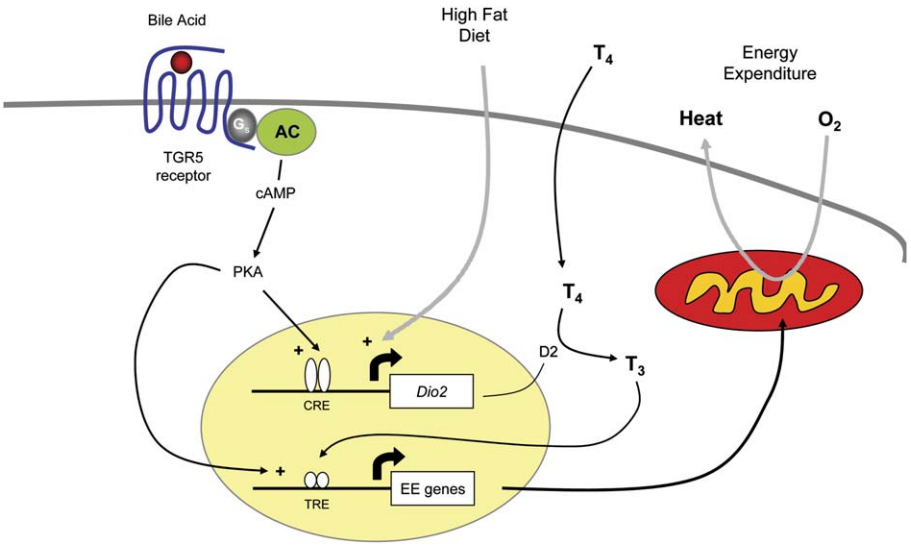


**Figure 1.** Role of bile acids in metabolism

An FXR-independent mechanism for BA action is shown. These pathways are active in thermogenically important tissues such a murine brown adipose tissue and human skeletal muscle due to coexpression of TGR5 and D2. TGR5 signaling generates intracellular cAMP, via $G_s$ activation of adenyl cyclase (AC), which subsequently activates *Dio2* gene expression through a classic cAMP response element (CRE). It is also possible that the TGR5 signaling pathway could also directly activate expression of certain EE gene products. The precise mechanism whereby locally generated $T_3$ activates oxygen consumption and EE in these tissues is unclear but could involve direct activation of EE genes by binding to thyroid hormone receptors found on thyroid hormone response elements (TREs). *Dio2* gene expression is activated by a high-fat diet distal to cAMP generation, although the exact location of the effect is unknown.

unexplained deaths, which led to its withdrawal from the market. Thyroid hormone treatment for weight loss has also been tried for decades. Unlike DNP, though, thyroid hormone treatment increased both urinary nitrogen excretion and heart rate; the former is thought to explain the muscle weakness found in states of thyroid hormone excess. Thus, thyroid hormone actions overlap with, but are not identical to, those observed with mitochondrial uncouplers and include the possibility of muscle wasting. Moreover, while local $T_3$ generation is clearly necessary for the EE response, it may not be sufficient. For example, $T_3$ could act by binding to nuclear $T_3$ receptors to directly or indirectly increase genes involved in EE, but this effect may also require activation of the cAMP signaling pathway, as suggested from studies in brown adipose tissue (for review, see Bianco et al. [2002]). Finally, in addition to inducing expression of D2 and UCPs, BAs also increase expression of genes involved in fatty acid metabolism as well as those that control expression of metabolic genes by functioning as transcriptional coactivators.

Given what we now know about this novel action of BAs, could they be used as a weight loss drug in humans? If it can be proven in clinical studies that skeletal muscle is the only significant metabolic target of BAs in man, then their use may provide a way to boost EE in muscle without increasing overall thyroid hormone action. One would need to be certain, though, that fat, not protein, was the fuel used by muscle to meet the increase in EE. The overall safety of BAs would also need to be established, as they are potentially hepatotoxic. Furthermore, it is unclear what effect BAs would have in tissues that express TGR5 but not D2, such as the heart, lung, kidney, liver, and spleen. Regardless, this new and exciting connection between BAs and $T_3$, two unlikely partners in weight loss, opens a new chapter in metabolic regulation of body weight.

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**Selected reading**

Bianco, A.C., Salvatore, D., Gereben, B., Berry, M.J., and Larsen, P.R. (2002). Endocr. Rev. *23*, 38–89.

Harper, J.A., Dickinson, K., and Brand, M.D. (2001). Obes. Rev. *2*, 255–265.

Hesselink, M.K., and Schrauwen, P. (2005). Horm. Metab. Res. *37*, 550–554.

Kalaany, N.Y., and Mangelsdorf, D.J. (2005). Annu. Rev. Physiol. *68*, 10.1146/annurev.physiol.68.033104.152158.

Kawamata, Y., Fujii, R., Hosoya, M., Harada, M., Yoshida, H., Miwa, M., Fukusumi, S., Habata, Y., Itoh, T., Shintani, Y., et al. (2003). J. Biol. Chem. *278*, 9435–9440.

Maruyama, T., Miyamoto, Y., Nakamura, T., Tamai, Y., Okada, H., Sugiyama, E., Nakamura, T., Itadani, H., and Tanaka, K. (2002). Biochem. Biophys. Res. Commun. *298*, 714–719.

Ravussin, E., Lillioja, S., Anderson, T.E., Christin, L., and Bogardus, C. (1986). J. Clin. Invest. *78*, 1568–1578.

Ribeiro, M.O., Carvalho, S.D., Schultz, J.J., Chiellini, G., Scanlan, T.S., Bianco, A.C., and Brent, G.A. (2001). J. Clin. Invest. *108*, 97–105.

Watanabe, M., Houten, S.M., Mataki, C., Christoffolete, M.A., Kim, B.W., Sato, H., Messaddeq, N., Harney, J.W., Ezaki, O., Kodama, T., et al. (2006). Nature, in press. Published online January 8, 2006. 10.1038/nature04330.

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